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Highly Active Platinum Catalysts for Nitrile and Cyanohydrin Hydration: Catalyst Design and Ligand Screening via High-Throughput Techniques

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ABSTRACT: Nitrile hydration provides access to amides that are indispensable to researchers in chemical and pharmaceutical industries. Prohibiting the use of this venerable reaction, however, are 1) the dearth of biphasic catalysts that can effectively hydrate nitriles at ambient temperatures with high turnover numbers, and 2) the unsolved challenge of hydrating cyanohydrins. Herein, we report the design of new "***donor-acceptor***"-type platinum catalysts by precisely arranging electron-rich and electron-deficient ligands *trans* to one other, thereby enhancing both the nucleophilicity of the hydroxyl group and the electrophilicity of the nitrile group. Leveraging a high-throughput, automated workflow and evaluating a library of bidentate ligands, we have discovered that commercially available, inexpensive DPPF [1,1'-ferrocenendiyl-bis(diphenylphosphine)] provides superior reactivity. The corresponding "*donor-acceptor*"-type catalyst **2a** is readily prepared from (DPPF)$PtCl_2$, PMe_2OH and AgOTf. The enhanced activity of **2a** permits the hydration of a wide range of nitriles and cyanohydrins to proceed at 40 ℃ with excellent turnover numbers. Rational reevaluation of the ligand structure has led to the discovery of modified catalyst **2c**, harboring the more electron-rich 1,1'-bis[bis(5-methyl-2-furanyl) phosphino] ferrocene ligand, which demonstrates the highest activity towards hydration of nitriles and cyanohydrins at room temperature. Finally, the correlation between the electron-donating ability of the phosphine ligands with catalyst efficiencies of **2a**, **2c**, **2d** and **2e** in the hydration of nitrile **7** are examined, and the results support the "*donor-acceptor*" hypothesis.

INTRODUCTION

In the field of chemistry, hydration is a term describing a transformation where water is added across a functional group, resulting in the addition of a hydroxyl group (HO^-) to one end and a proton (H^+) to the other. Due to its inherent green characteristics and atom economy, this process is desirable for generating industrially useful products, for instances, olefin and nitrile hydration produce valuable alcohol and amide commodity chemicals.[1,2] Furthermore, the hydration reaction generally proceeds in a biphasic (aqueous and organic) solvent system; however, the majority of transition metal catalysts cannot survive reactions performed in water and thus require storage under inert atmosphere and necessitate specialized equipment. For this reason, developing new highly efficient and catalytic hydration reactions still remains a challenge.[3]

Amides are key intermediates in the fine chemical and polymer industries; for instance, there are many different widely used nylons that are made from polymers derived from amides.[4] Hydration of nitriles is the simplest and most direct way to produce amides and thus there is a compelling need to develop practical and biphasic catalysts to efficiently hydrate nitriles, particularly cyanohydrins.[5,6] Although transition metal-catalyzed selective hydration of nitriles has been reported with the use of cobalt (Co),[7,8] molybdenum (Mo),[9] iridium (Ir),[10] rhodium (Rh),[11,12] ruthenium (Ru),[13-15] platinum (Pt)[16-18] and nickel (Ni),[19] the harsh conditions and low turnover numbers (for sterically hindered nitriles) impede the general applicability of these catalysts (Figure 1-A). Seminal work was achieved by Parkins and coworkers with the discovery of $HPt[(PMe_2O)_2H](PMe_2OH)$ (**1a**) in 1995, and since then, hydration of nitriles by platinum complexes has become a powerful synthetic tool.[20,21] Several recent reports have utilized the nitrile hydration catalyzed by **1a** to unveil an amide functional group in the context of complex molecule synthesis.[22-24] However, **1a** generally requires elevated temperatures (80-100 ℃) and the catalyst loading is frequently increased to 10-25 mol % to expedite the reaction. Furthermore, limited success has been achieved in cyanohydrin hydration (Figure 1-B). For example, Parkins catalyst (**1a**), which has proven to be the most reactive and versatile in nitrile hydration, demonstrates very low efficiency for hydration

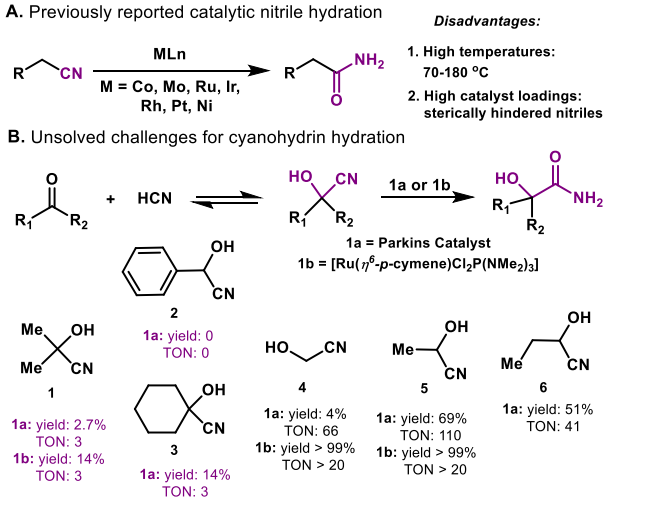


Figure 1. Hydration of nitriles and cyanohydrins

of cyanohydrins; only two cyanohydrins, lactonitrile (**5**) and 2-hydroxybutyronitrile (**6**), can be hydrated by **1a**.[25] Further studies revealed that HCN, generated by dissociation of cyanohydrins, irreversibly binds to **1a**, is responsible for deactivation of the catalyst with cyanohydrin substrates.[26] In 2012, a new catalyst [Ru(η^6-*p*-cymene)Cl_2P(NMe_2)$_3$] (**1b**) was reported to hydrate glycolonitrile (**4**) and lactonitrile (**5**) with complete conversion.[27] However, the catalytic hydration of cyanohydrins, especially ketone-derived cyanohydrins, still remained a long pursued but unsolved challenge.[28]

There are three dimethylphosphine oxide ($Me_2HP{=}O$, existing in equilibrium with its phosphinous acid form PMe_2OH) ligands arranged in the Parkins catalyst (**1a**); two of them are associated by hydrogen bonding, while the third dimethylphosphine oxide at Pt that is *trans* to one of the other two provides a free hydroxyl nucleophile to attack the nitrile (Figure 2-A).[20,21] We envisioned that the two bridging PMe_2OH functioned as a masked bidentate ligand through hydrogen bonding, and stabilized the entire Pt-complex. As a result, introducing an electron-rich bidentate ligand instead of two bridging PMe_2OH ligands and an electron-deficient dimethylphosphine oxide on platinum center will form a "*donor-acceptor*"-type catalyst. Furthermore, the platinum, which inherently adopts square planar geometry, would precisely make the electron-rich and electron-deficient ligands *trans* to each other in a nearly linear arrangement, and therefore serves as a platform to realize the "*donor and acceptor*" property of the catalyst. We assumed the key features that would enable these new catalysts to accelerate nitrile hydration and even solve the challenge of cyanohydrin hydration are: 1) the electron-donating nature of the bidentate ligand would significantly enhance the nucleophilicity of the hydroxyl group in the *trans* PMe_2OH ligand; 2) the "*donor-acceptor*" system could afford a more polarizable catalyst,[29] thus facilitating the activation of nitriles.[30] Herein, we report new designed "*donor-acceptor*"-type platinum catalysts that are highly effective in hydrating both nitriles and cyanohydrins at lower temperatures with excellent turnover numbers (Figure 2-B). Several optimal donor ligands of the ferrocenyl-phosphine family were identified by high-throughput screening of a library of bidentate ligands. Based on the screening results, the most highly active catalyst **2c** was discovered by turning to the more electron-donating 1,1'-bis[bis(5-methyl-2-furanyl) phosphino] ferrocene ligand. This robust catalyst can hydrate nitriles and more importantly, cyanohydrins, at room temperature with good to excellent turnover numbers.

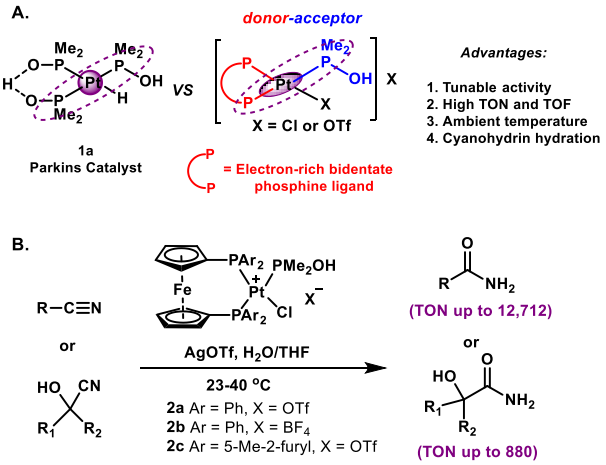


Figure 2. Our designed "*donor-acceptor*" catalysts and their high activities in nitrile and cyanohydrin hydration

RESULTS AND DISCUSSION

Our strategy to identify the optimal "*donor-acceptor*"-type catalysts is outlined in Figure 3. The evaluation of bidentate ligands proceeded by assessing the feasibility of hydrating hydrocinnamonitrile (**7**), and the screening was conducted using high-throughput techniques (Figure 3-A).[31] Complexes with the structure (L_1~L_2)Pt(PMe_2OH)$(OTf)_2$ were generated from a panel of 42 representative chiral and achiral bidentate ligands, along with commercially available (COD)$PtCl_2$, PMe_2OH and AgOTf. Our designed procedure is described as follows: a stock solution of (COD)$PtCl_2$ was added to the panel of 42 vials, each of which contained one bidentate ligand. The corresponding (L_1~L_2)$PtCl_2$ complexes generated were then treated with stock solutions of dimethylphosphine oxide and AgOTf. The 42 "*donor-acceptor*"-type catalysts, in the form of (L_1~L_2)Pt(PMe_2OH)$(OTf)_2$, were thus generated *in situ* and their activities towards nitrile hydration were evaluated by adding a stock solution of nitrile **7**. After 10 minutes, the mixtures were analyzed by LC-MS. To our delight, a number of bidentate phosphine ligands exhibited excellent activity (> 60% conversion) within 10 minutes at 40 ℃ (Figure 3-B). In general, *bis*-aryl-substituted phosphine ligands provided optimal conversions; for instance, (*S*)-SDP [(*S*)-7,7'-bis(diphenylphosphino)-1,1'-spirobiindane], (*S*,*S*)-BDPP [(*2S*, *4S*)-2,4-Bis(diphenylphosphino)pentane and (–)-DIOP [(*4R*, *5R*)-(–)-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1.3-dioxolane] afforded 72%, 69% and 66% conversion, respectively. Additionally, more electron-rich ligands exhibit higher reactivity; for examples, Josiphos SL-J005-1 [*R*)-1-[(S_P)-2-(Diphenylphosphino)ferrocenyl]ethyldi(3,5-xylyl)phosphine] affords 49% conversion while SL-J015-1 [(*R*)-1-{(S_P)-2-[Di(2-furyl)phosphino]ferrocenyl}ethyldi(3,5-xylyl)phosphine] gave a higher conversion of 65% under identical conditions. We were also pleased to find that the commercially available, inexpensive ferrocenyl phosphine ligand, DPPF [1,1'-ferrocenendiyl-bis(diphenylphosphine)], achieved the second highest activity towards hydration of **7** (69% conversion).

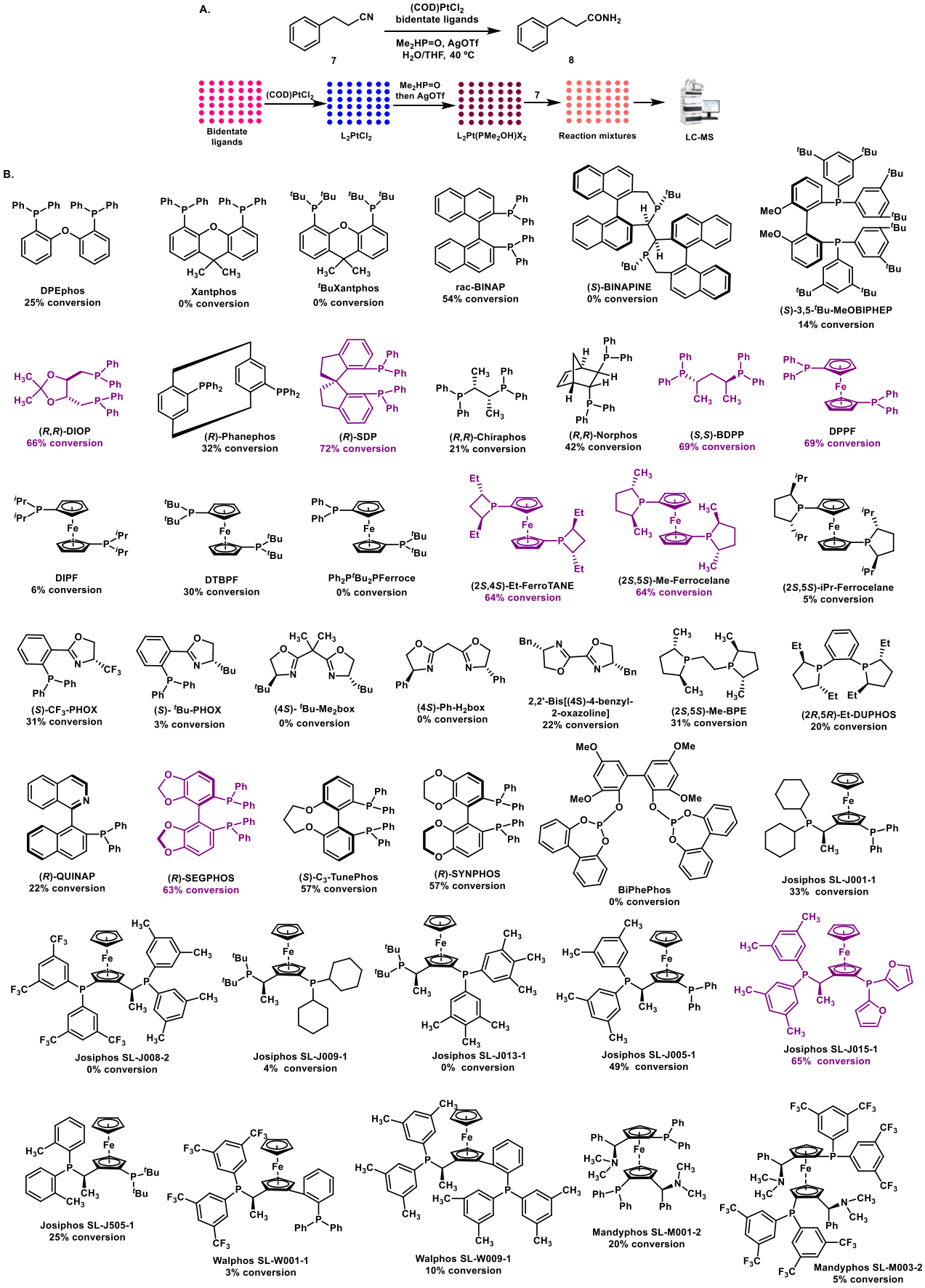
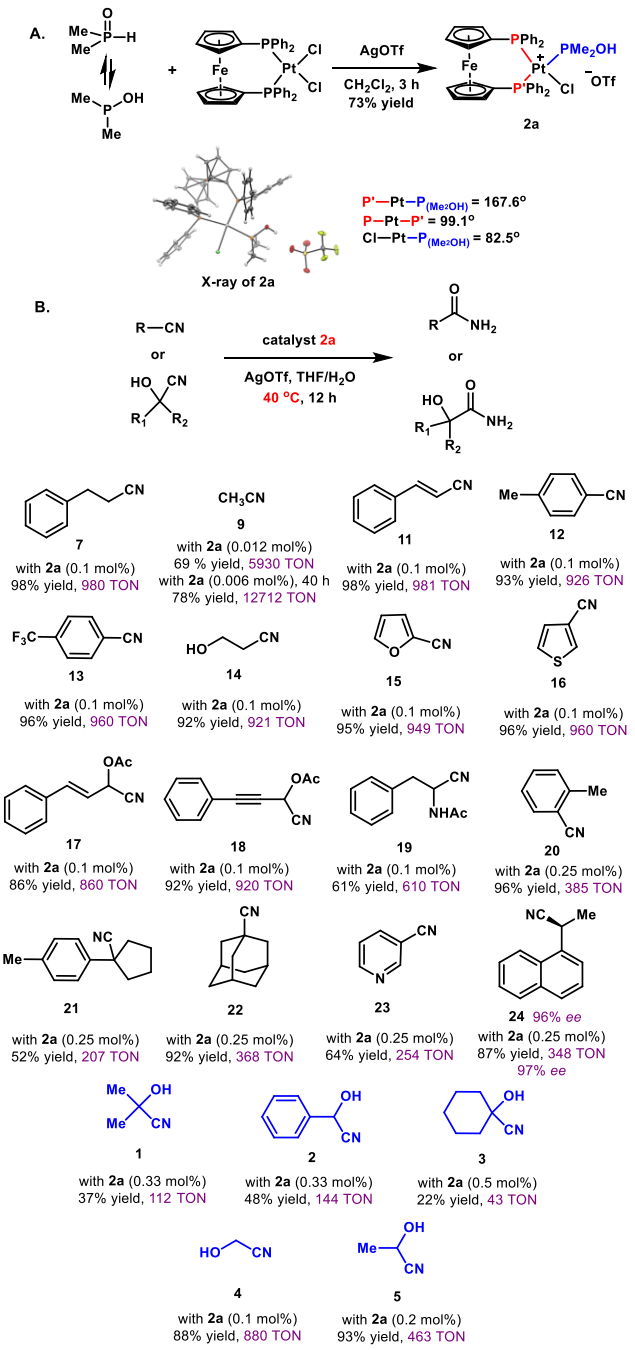


Figure 3. Screening of bidentate ligands via high-throughput techniques: (A) Schematic representation of the experimental process (B) Structures of 42 bidentate ligands and their corresponding conversions in this high-throughput experiment

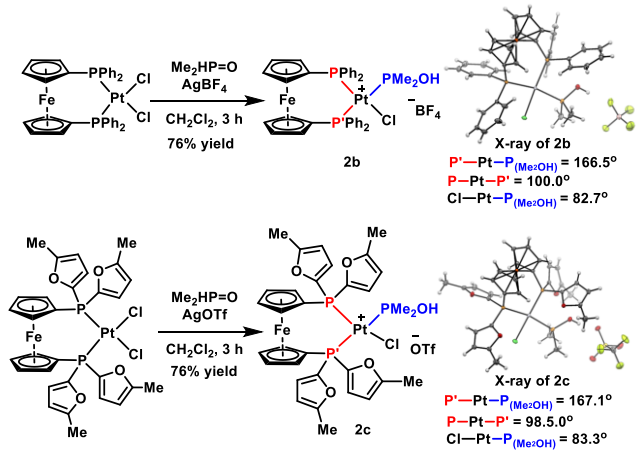
Scheme 1. A "*donor-acceptor*"-type catalyst 2a and its high activity towards hydration of a wide range of nitriles and cyanohydrins



In light of these screening results, the DPPF-based platinum catalyst **2a** was synthesized (Scheme 1-A). We established that the reaction of (DPPF)$PtCl_2$ with dimethylphosphine oxide and AgOTf at room temperature for 3 h affords the air-stable crystalline solid **2a**.[32,33] The activity of the newly synthesized "*donor-acceptor*"-type catalyst was evaluated by performing the hydration of different nitriles and cyanohydrins at 40 ℃ (Scheme 1-B). The catalytic protocol exhibits considerable scope. Reactions with various nitriles, including those that are sterically hindered (for example, **20**, **21**, and **22**), were generally conducted with 0.1-0.25 mol % catalyst **2a**, and full conversions were readily achieved at 40 ℃ in 12 hours. The corresponding amides were isolated in excellent yields, demonstrating impressive turnover numbers. Catalyst **2a** also exhibits high selectivity towards nitriles in the presence of alkenes and alkynes (**11**, **17** and **18**). Furthermore, turnover numbers in the hydration of acetonitrile (**9**) are as high as 12,712 by catalyst **2a** at 40 ℃ for 40 h, more than twice the previously reported maximum turnover number as 5,700 by Parkins Catalyst (**1a**).[21] We were pleased to find that enantiomerically enriched nitrile **24** does not lose the stereochemical fidelity under the hydration condition.[34] Prior difficulties associated with the hydration of cyanohydrins stem from the rapid liberation of cyanide at higher temperatures thus poisoning noble metal catalysts.[26] As a result, there have been no nitrile hydration catalysts capable of converting cyanohydrins to their hydration products with good turnover numbers. To our delight, the catalytic hydration of cyanohydrins, including **1** and **3** that had yet succumb to hydration, was achieved by 0.1-0.5 mol % of catalyst **2a** with good yields and excellent turnover numbers.

With these results in hand, further modification of catalyst **2a** was attempted through the preparation of catalysts **2b** (with tetrafluoroborate as the counter ion) and catalyst **2c** (with a more electron-donating 1,1'-bis[bis(5-methyl-2-furanyl)phosphino]ferrocene ligand) (Scheme 2). The X-ray structures of these complexes show that the diarylphosphinoferrocene bound cationic platinum center retains a nearly flat, square planar coordination geometry. The P'−Pt−$P_{(Me_2OH)}$ angles in **2a**, **2b** and **2c** are 167.6 °, 166.5 ° and 167.1 °, respectively, which indicate the near linear orientation of P'−Pt−$P_{(Me_2OH)}$. This arrangement would benefit the "*donor-acceptor*" interaction between P'−Pt bond and Pt−$P_{(Me_2OH)}$ bond, thus enhancing the nucleophilicity of the hydroxyl group in PMe_2OH ligand towards nitriles. In addition, the ferrocenyl ligand is twisted by 29 ° in order to present the two phosphorus atoms to platinum with a relatively large 100 ° P–Pt–P' bite angle; as a consequence, the Cl−Pt−$P_{(Me_2OH)}$ angle becomes compressed in these complexes which may reveal another reason for the enhancement of the activity of these catalysts towards nitrile hydration.

Scheme 2. Modified catalysts 2b and 2c



For comparison, the efficiency of catalysts **2a–c** and Parkins catalyst (**1a**) were assessed in the hydration of 20 equivalents of nitrile **7** (Figure 4-A). Catalyst **2a** without any additive has already exceeded the rate of nitrile hydration observed by **1a** at 40 ℃. Upon addition of 1 equivalent of corresponding silver salt to abstract the chloride ligand, both catalysts **2a** and

2b show dramatically enhanced activity towards hydration of **7** at 40 ℃. Notably, catalyst **2c**, which contains a more electron-rich ligand, provides full conversion of **7** within 10 minutes at room temperature. This represents a >30-fold acceleration in the rate of hydration relative to **1a**. Catalysts **2a** and **2c** also allows the hydration reaction of acetonitrile (**9**) to proceed with significantly higher turnover numbers than previously observed for Parkins catalyst (**1a**) (Figure 4-B). **2a** and **2c**, assisted by 1 equivalent of AgOTf, are distinguished catalysts for hydration of acetonitrile (**9**) with respective turnover numbers of 1,790 and 4,457, while Parkins catalyst (**1a**) only provides a turnover number of 81 under otherwise identical condition. Furthermore, hydration of **9** at room temperature by catalyst **2c** without any additive still provides a turnover number as high as **695**, which is nine times of that observed for **1a**.

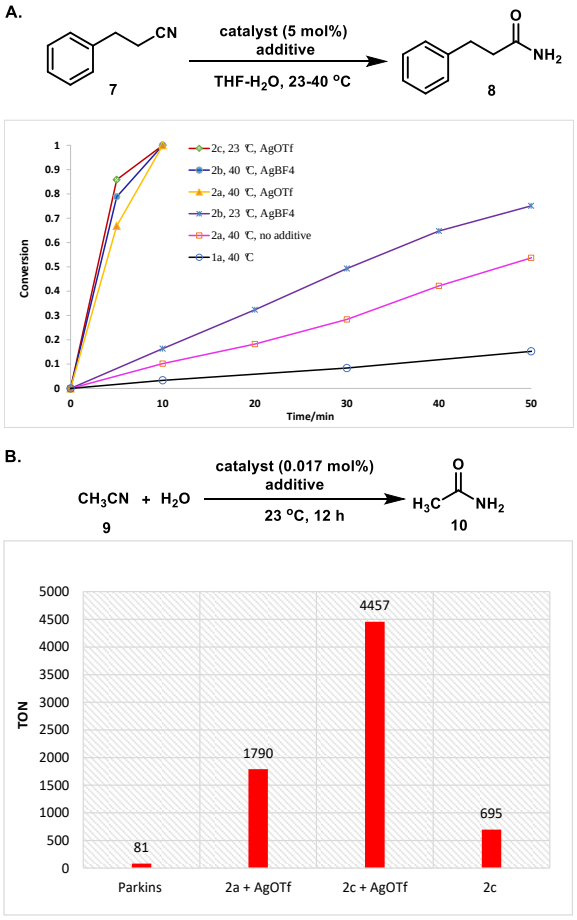
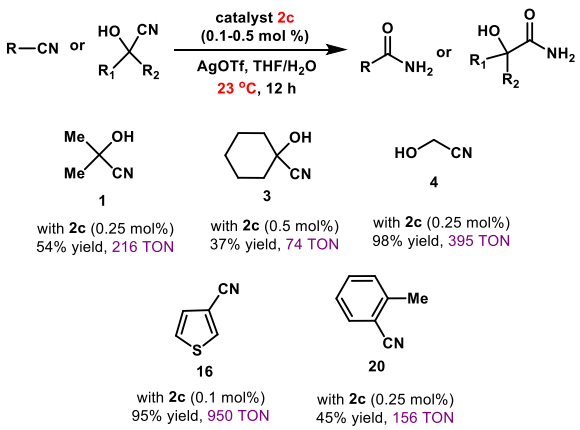


Figure 4. Comparing the performance of Parkins catalyst (1a) with 2a–c in nitrile hydration (A) Reactions were performed by dissolving catalyst (5 mol %) with or without 1 equivalent silver additive followed by addition of **7** in H_2O (0.5 mL) and THF (0.5 mL). While stirring at 23 ℃ or 40 ℃, aliquots were sampled by LC-MS analysis versus internal standard. (B) Reactions were performed by dissolving catalyst (0.017 mol %) with or without 1 equivalent AgOTf followed by adding acetonitrile (**9**) (60.0 mmol, 3.2 mL) and H_2O (1.1 mL). After stirring at 23 ℃ for 12 h, the solvent was removed to provide acetamide **10** as a white solid.

Catalyst **2c** displays noticeably increased catalytic activity, and therefore hydrations of both nitriles (**16** and **20**) and cyanohydrins (**1**, **3** and **4**) were achieved at room temperature with good turnover numbers (Scheme 3). This hydration occurs under conditions at which the dissociation of cyanohydrins to the corresponding ketone and hydrogen cyanide is slow enough to maintain the integrity of the catalyst. To the best of our knowledge, **2c** is the first catalyst that realizes cyanohydrin hydration at room temperature.

Scheme 3. Hydration of nitriles and cyanohydrins by 2c with high efficiency at room temperature



Finally, in order to evaluate the "*donor-acceptor*" system in which the more electron-rich group in the donor part would increase the activity of the catalysts thus accelerting the reactions, we synthesize catalysts **2d** and **2e**, and compare their efficiencies with **2a** and **2c** in hydration of **7** (Figure 5). To our delight, the plots show that more electron-donating ligands result in increasing activities of the catalysts, which match the "*donor-acceptor*" design. As previously observed, **2c** that contains the most electron-donating ligand in the four catalysts provides full conversion of **7** in 10 minutes at room temperature. **2d** that consists of an electron-deficient ligand{1,1'-bis[bis(4-(trifluoromethyl)phenyl)phosphino]ferrocene} exhibits decreased activity, offering full conversion after 1 hour. Furthermore, **2e** with a more electron-deficient ligand {1,1'-bis[bis(3,5-(trifluoromethyl)phenyl)phosphino]ferrocene} provides only 45% conversion after 50 minutes and the reaction stalls after 15 hours. [34]

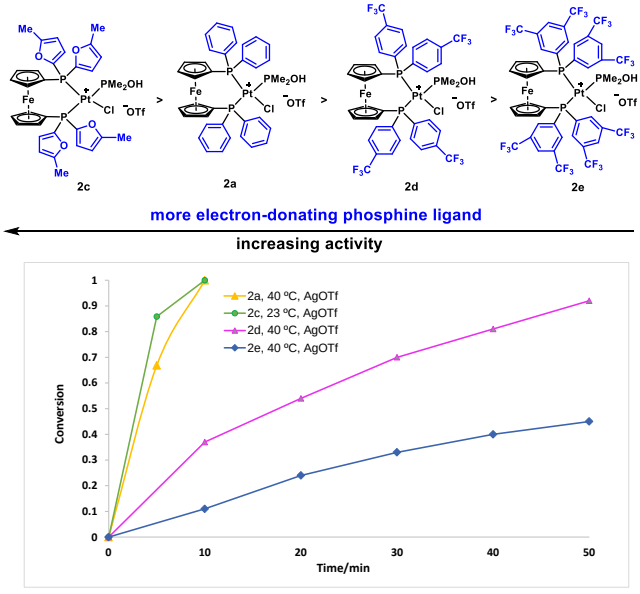


Figure 5. Examination of the relationship between the electron-donating ability of the phosphine ligands with the activity of the catalysts 2a, 2c, 2d and 2e in the hydration of 7.[35]

CONCLUSIONS

The above findings illustrate that the newly synthesized "*donor-acceptor*"-type catalyst **2c** is superior towards hydration of nitriles and cyanohydrins from two characteristics. First, it can promote nitrile hydration at room temperature with good turnover numbers. Second, due to its high activity at ambient temperature, hydration of cyanohydrins can be achieved by **2c** with high efficiency. These attributes distinguish catalyst **2c** not only from the most effective nitrile hydration catalysts reported to date, such as Parkins catalyst (**1a**), but also from the other types of ferrocenyl-phosphine platinum catalysts **2a**, **2b**, **2d** and **2e**, which have likewise surpassed **1a** in the hydration of both nitriles and cyanohydrins. Ongoing research pursuits in this filed include discovering more practical and inexpensive catalysts that can be utilized in industry, and the incorporation of chiral bidentate phosphine ligands in related new "*donor-acceptor*"-type catalysts for the development of asymmetric protocols by the means of nitrile and cyanohydrin hydrations.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and characterization data (^{1}H and ^{13}C NMR, HRMS) for all new compounds (PDF)

Crystallographic information for **2a** (CIF)

Crystallographic information for **2b** (CIF)

Crystallographic information for **2b** (CIF)

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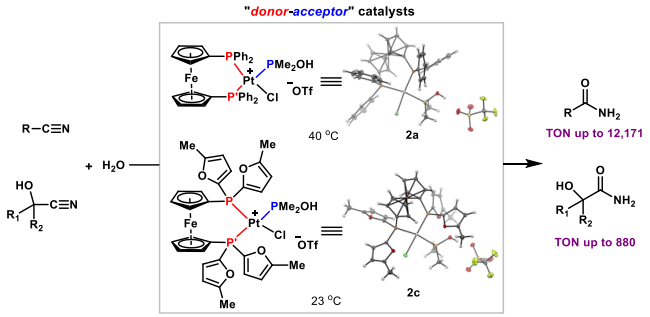
(35) Please see the "Supporting Information" for the details of the experiment.


"donor-acceptor" catalysts
R–C≡N
+ H2O
HO
R1
R2
C≡N
PPh2
Fe
Pt
PMe2OH
Cl
OTf
40 °C
2a
Me
O
P
23 °C
2c
O
R
NH2
TON up to 12,171
HO
TON up to 880